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A mixed lithium-cadmium amide and a combination of lithium and zinc amides were reacted with a range of ferrocenes; deprotonative mono- or di-metallation in general occurred chemoselectively at room temperature, as evidenced by subsequent quenching with iodine.

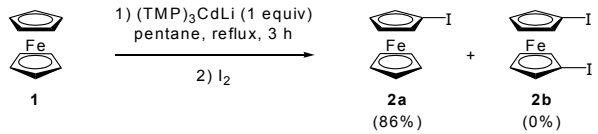
Metallocenes have met an important development. Ferrocene has notably been extensively used to synthesize a variety of derivatives with applications ranging from catalysis[1] to materials science[2] and bioorganometallic chemistry.[3]

Among the methods used to functionalize ferrocene compounds, deprotonative metallation plays an important role.[4] The presence of a substituent containing heteroatoms on ferrocene usually directs deprotonation to the adjacent position, giving after subsequent quenching 1,2-unsymmetrical ferrocenes. The reagents classically used for this purpose are lithium bases, which are highly polar reagents, hardly tolerating the presence of reactive functional groups. For these reasons, restricted conditions such as low temperatures or solvents of low polarity have to be used in order to ensure good results, when attained.

In recent studies, ferrocene was mono- or poly-metallated using mixed alkali metal-magnesium, -zinc, and -manganese bases, and the species isolated were studied by X-ray diffraction.[5] Another mixed lithium-magnesium base, TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidino), allowed chemoselective deprotonation reactions of ferrocenes bearing an ester, a nitrile and a carboxylic acid function, when used in a polar solvent at temperatures around 0 °C.[6]

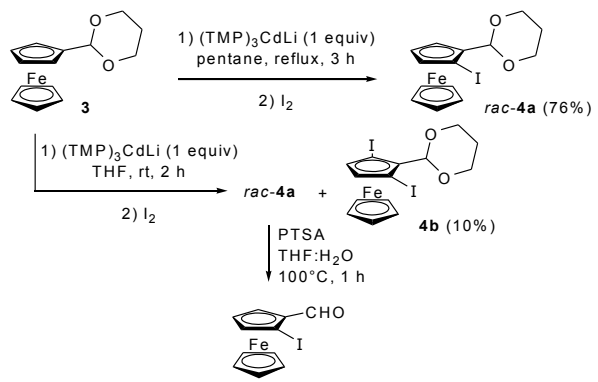
Among recently documented non cryogenic alternatives for the deprotonative metallation of aromatics,[5] *in situ* prepared mixtures of $ZnCl_2 \cdot TMEDA$[7] (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), or $CdCl_2 \cdot TMEDA$,[8] and 3 equivalents of LiTMP proved efficient for the functionalization of a large range of ferrocene substrates including aromatics bearing reactive functions and sensitive heterocycles. Hence we decided to attempt their use in the ferrocene series.

It is known[9] that ferrocene can be lithiated using 2 equiv of *tert*-butyllithium in the presence of 0.1 equiv of potassium *tert*-butoxide in THF (tetrahydrofuran) at –75 °C. The lithium-cadmium base, which can be considered as $(TMP)_3CdLi$,[8] was first chosen to attempt the metallation of ferrocene (**1**). When treated with 0.5 or 1 equiv (with respect to Cd) of $(TMP)_3CdLi$ in THF at room temperature for 2 h, ferrocene (**1**) remained unchanged, as demonstrated by subsequent quenching with iodine. In contrast, when the deprotonation step was carried out using 1 equiv of base at the reflux temperature of pentane for 3 h, the iodide **2a** was isolated in 86% yield (Scheme 1).



Scheme 1 Deprotonative cadmiation of ferrocene

In the presence of a chelating group, the same reaction is favoured. Thus, the similar functionalization of the acetal **3** can be performed either at the reflux temperature of pentane to afford the acetal-protected iodide **4a** in 76% yield, or at room temperature in THF to give, after subsequent deprotection of the aldehyde, the derivative **5a** in 51% overall yield. When THF was the solvent, the 2,5-diodo derivative **4b** was also formed in 10% yield (Scheme 2). It is pertinent to mention that lithium bases were previously used to deprotonate the acetal **3**, albeit at lower temperatures in order to prevent substantial cleavage of the dioxane ring.[10]

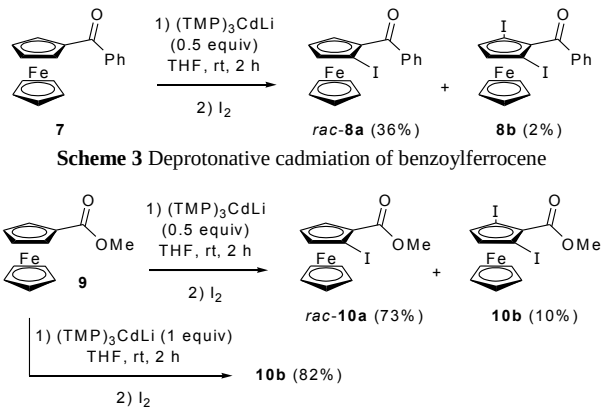


Scheme 2 Deprotonative cadmiation of 2-ferrocenyl-1,3-dioxane

In order to check the chemoselectivity of reactions using $(TMP)_3CdLi$, the metallation of ferrocene ketones was attempted. Starting from acetylferrocene (**6**) logically resulted in THF or pentane in a complex mixture presumably due to the presence of acidic α-protons. From benzoylferrocene (**7**), it proved possible using 0.5 equiv of base in THF at room temperature for 2 h to isolate the mono- and diiodide **8a**,**b** in 36 and 2% yield, respectively (Scheme 3).

We then turned to methyl ferrocenecarboxylate (**9**), which

should be less sensitive than ketones **6**,**7**. Indeed, employing only 0.5 equiv of base resulted in the formation of the mono- and diiodide **10a**,**b** in 73 and 10% yield, respectively. Reaction times of 0.5 and 4 h did not modify significantly the yields. The dimetallation could be favoured using 1 equiv of base, to furnish the diiodide **10b** in 82% yield (Scheme 4).



Scheme 4 Deprotonative mono- and dicadmiation of methyl ferrocenecarboxylate

The structure of the latter was determined unequivocally by X-ray diffraction analysis of crystals obtained by slow evaporation of a dichloromethane solution (Figure 1).†

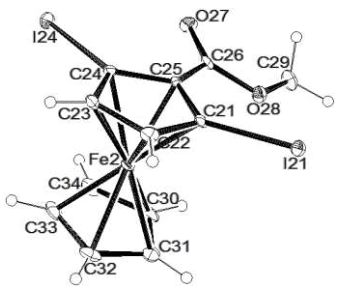
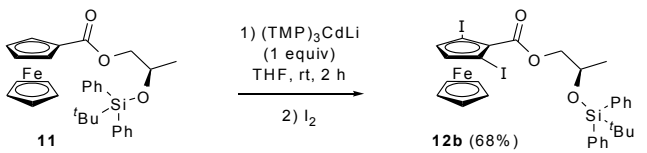


Figure 1 ORTEP diagram (30% probability) of the diiodide **10b**.

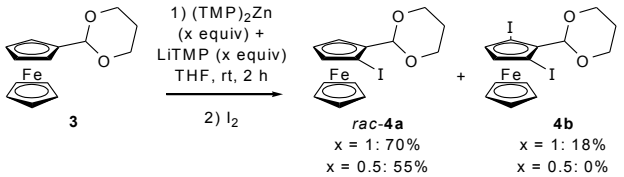
This possibility was successfully extended to the ferrocenecarboxylate **11**, for which the corresponding diiodides **12b** was isolated in a satisfying yield (Scheme 5).



Scheme 5 Deprotonative dicadmiation of ferrocenecarboxylates **11-13**

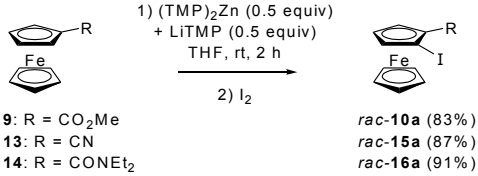
The base *in situ* prepared from $ZnCl_2$·TMEDA and 3 equivalents of LiTMP, which can be considered as a 1:1 mixture of $(TMP)_2Zn$ and LiTMP,[7] was then chosen to attempt the metallation of some ferrocene compounds. Bare ferrocene (**1**) remained unchanged when treated at room temperature in THF with the lithium-zinc base. Exchanging THF for pentane and carrying out the reaction at reflux resulted in the formation of a mixture of monoiodide **2a**, 1,1'-diiodide **2b** and unreacted ferrocene (**1**). This contrasts with what has been obtained using $(TMP)_3CdLi$, and showed that the lithium-cadmium base is more efficient for the functionalization of bare ferrocene.

In the case of the acetal **3**, as previously observed using $(TMP)_3CdLi$, a mixture of the mono- and the diiodide **4a**,**b** (80:20 ratio) was obtained using 1 equiv of $ZnCl_2$·TMEDA and 3 equiv of LiTMP in THF at room temperature. Dividing by two the amount of base allowed to discard the diiodide **4b**, but to the detriment of the conversion (Scheme 6).



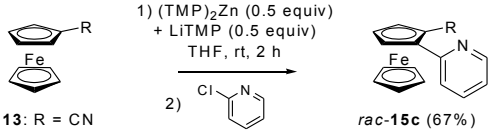
Scheme 6 Deprotonative zincation of 2-ferrocenyl-1,3-dioxane

In the presence of electron-withdrawing substituents, the ferrocene ring can be efficiently deprotonated using the *in situ* generated mixture of $(TMP)_2Zn$ (0.5 equiv) and LiTMP (0.5 equiv). From the ferrocene ester **9**, the monoiodide **10a** was selectively obtained, and isolated in 83% yield (the ^1H NMR spectra showed that remaining starting material was the only impurity present in the crude). The dideprotonation was similarly not observed when cyanoferrocene (**13**) and *N*,*N*-diethylferrocenecarboxamide (**14**) were involved in the reaction, and the expected iodides **15a** and **16a** were isolated in 87 and 91% yield, respectively (Scheme 7).



Scheme 7 Deprotonative zincation of methyl ferrocenecarboxylate, cyanoferrocene and *N*,*N*-diethyl ferrocenecarboxamide

Deprotonative zincation of aromatic compounds followed by *in situ* palladium-catalyzed cross-coupling of the lithium zincate such generated constitutes a straightforward access to biaryl compounds.[7] Using catalytic amounts of $PdCl_2$ as palladium source and 1,1'-diphenylphosphinoferrocene (dppf) as ligand with 2-chloropyridine allowed the synthesis of the pyridine derivatives **15c** and **16c** in satisfying yields (Scheme 8). The structure of the compound **15c** was determined unequivocally by X-ray diffraction analysis (Figure 2).†



Scheme 8 Deprotonative zincation of cyanoferrocene and *N*,*N*-diethylferrocenecarboxamide followed by cross-coupling

Monometallation mediated by the lithium-zinc base also proved possible for methyl ferrocene-1,1'-dicarboxylate (**17**). Under the same reaction conditions, the iodide **18a** was obtained in 72% yield. Unfortunately, using 1 equiv of $(TMP)_3CdLi$ with this substrate failed in only giving one

diiodide. Indeed, two diiodides (compounds **18b**) and even a triiodide (**18c**) were isolated from the complex mixture obtained (Scheme 9).

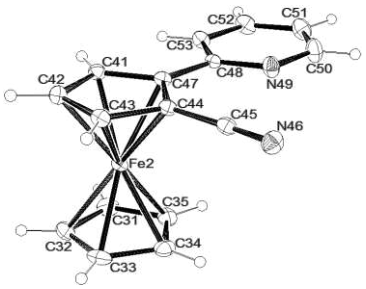
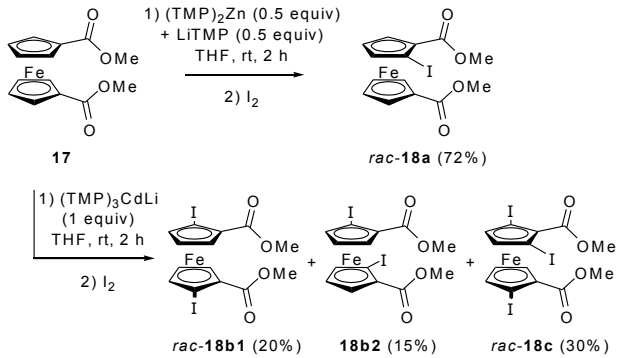
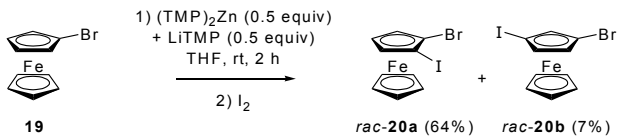


Figure 2 ORTEP diagram (30% probability) of the compound **15c**.



Scheme 9 Deprotonative metallation of methyl ferrocene-1,1'-dicarboxylate

Finally, the behaviour of bromoferrocene (**19**) towards the lithium-zinc base was considered. Under the conditions described above, 1-bromo-2-iodoferrocene (**20a**) was obtained as the main product (64% yield). 1-Bromo-3-iodoferrocene (**20b**) concomitantly formed, and was isolated in 7% yield (Scheme 10). Such a migration of a heavy halogen has previously been observed using lithium amides as metallating agents,[11] and could be explained herein by the presence of LiTMP in the basic mixture.



Scheme 10 Deprotonative zincation of bromoferrocene

The structure of the iodide **20a** was established on the basis of its NMR spectra, by comparison with previously reported data.[12] By slow evaporation of a dichloromethane solution of the iodide **20a**, it also proved possible to collect suitable crystals for X-ray diffraction analysis. The presence of bromo and iodo groups at adjacent positions was confirmed by this way. However, the analysis of the data was complicated by a phenomenon which could be interpreted by a partial enrichment in favour of one enantiomer during the crystallization (Figure 3).†

In summary, $(TMP)_3CdLi$ is an efficient reagent, allowing the monodeprotonation of weakly activated ferrocenes and the dideprotonation of ferrocenes activated by an ester function. The corresponding Li-Zn base is more suitable for the room temperature monofunctionalization of activated ferrocenes.

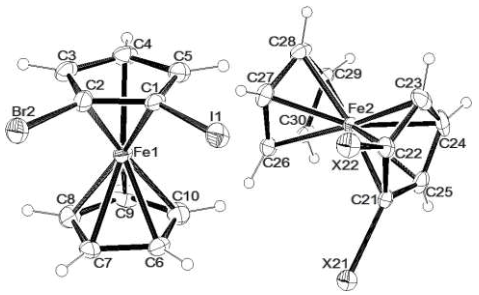


Figure 3 ORTEP diagram (30% probability) of the iodide **20a**: main enantiomer (left) and racemic mixture (right, X21 = Br, X22 = I and X22 = Br, X21 = I)

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of compounds, CIF files of **10b** (CCDC 755178), **15c** (CCDC 755179) and **20a** (CCDC 755180). See DOI: 10.1039/b000000x/

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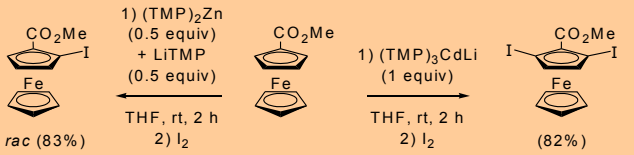

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